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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Confirmation No. 4581

PAGANELLI et al.

Atty. Ref.: 4865-17

Appln. No. 10/554,410

T.C. / Art Unit: 1643

Filed: November 17, 2005

Examiner: A. Gussow

FOR: MEDICAMENT FOR THE TWO-STEP PERIOPERATIVE THERAPY OF SOLID
TUMOURS

* * *

SUPPLEMENTAL RESPONSE

May 28, 2008

Mail Stop Amendment

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

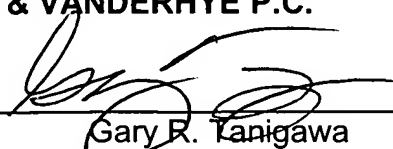
Further to the Amendment filed April 28, 2008, submitted herewith is a verified English translation of priority document, IT Application No. RM2003A000196, filed on April 24, 2003.

Applicants submit that the claims are in condition for allowance. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYTE P.C.

By: _____


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DECLARATION

I, Luisa Currado, hereby sincerely declare that I am conversant with the English and Italian languages and am a competent translator thereof, that to the best of my knowledge and belief the following is a true and correct translation in the English language of the priority document, i.e. Italian patent application for invention nRM2003A000196 filed on 24 April 2003.

Signed this 23 day of the month of April 2008

Luisa Currado



DECLARATION

I, Luisa Currado, hereby sincerely declare that I am conversant with the English and Italian languages and am a competent translator thereof, that to the best of my knowledge and belief the following is a true and correct translation in the English language of the priority document, i.e. Italian patent application for invention nRM2003A000196 filed on 24 April 2003.

Signed this 23 day of the month of April 2008

Luisa Currado

MINISTRY OF THE PRODUCTIVE ACTIVITIES
General Directorate of the Productive
Development and Competition
Italian Patent and Trademark Office
Office G2

duty stamp

Authentication of the copy of the documents relating to the patent application for: industrial invention
N. RM2003A000196

It is hereby declared that the attached copy is a true copy of the original documents filed
with the above-identified patent application, the data of which are given in the enclosed
official filing certificate.

Rome, March 15, 2004

(seal)

The Officer
Elena Marinelli
(signature)

TO MINISTRY OF COMMERCE AND HANDICRAFT
ITALIAN PATENT AND TRADEMARK OFFICE – ROME (I.P.T.O)
PATENT APPLICATION FOR INDUSTRIAL INVENTION, FILING OF SUBSEQUENT
DOCUMENTS, PRE-ACCESSIBILITY TO THE PUBLIC

FORM A

DUTY STAMP

A. APPLICANT(S)

1) Name SIGMA-TAU Industrie Farmaceutiche Riunite JN-Juridical Name SP (Stock Company)
Residence Rome (RM) code
2) Name JN-Juridical Name
Residence code

B. REPRESENTATIVE OF THE APPLICANT BEFORE THE I.P.T.O.

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C. ELECTIVE ADDRESS recipient

street n. city Postal Code (Province)

D. TITLE Proposed Class (Section/Class/Subclass) Group/Subgroup

"Use of reagents for the preparation of a medicine useful for the two stage perioperative
therapy of solid tumours"

PRE-ACCESSIBILITY TO THE PUBLIC: YES ☒ IF REQUEST: DATE / / PROTOCOL N°

E. DESIGNATED INVENTORS surname name surname name

1) Giovanni PAGANELLI 3) Umberto VERONESI
2) Paolo CARMINATI 4)

F. PRIORITY

nation or organization kind of priority application number filing date attached S/R SUBSEQUENT DOCUMENTS DISSOLUTION
DATE PROTOCOL N°

1) none
2)

G. RECOGNIZED AUTHORITY FOR THE DEPOSIT OF MICRO-ORGANISM CULTURES

name

H. SPECIAL REMARKS

duty stamp

ENCLOSED DOCUMENTS

N.items

Doc. 1) [1] PROV n.pag. 18 abstract with main drawing, description and claims (compulsory 1 item)
Doc. 2) [0] PROV n.sheets drawing (compulsory if cited in the description, 1 item)
Doc. 3) [1] RIS power of attorney, power or reference to general power

Doc. 4 [0] RIS designation of the inventor
Doc. 5 [0] RIS priority documents with Italian translation
Doc. 6 [0] RIS authorization or assignment deed
Doc. 7 [0] full name of the applicant

8) Certificates of payment, total euro Onehundredeightyeight/51

COMPILED THE 24/04/2003 Signature of Applicant(s)
Dott. Marco SPADARO

CONTINUES YES/NO ~~NO~~

A CERTIFIED COPY OF THE PRESENT DOCUMENT IS REQUIRED YES/NO ~~YES~~

CHAMBER OF COMMERCE INDUSTRY HANDICRAFT AND AGRICULTURE - ROME CODE 58

FILING RECEIPT APPLICATION NUMBER RM2003A000196

Year twothousandthree day twentyfour month of April

The above applicant(s) has/have submitted to the undersigned this application accompanied by No. [00] additional sheets for the granting of the above patent.

I. Various Remarks by the Recording Officer:

Filing Person	(stamp)	The Recording Officer
(signature illegible)		(signature illegible)

APPLICATION No RM2003A00019

REG A

FILING DATE 24/04/2003

PATENT No.

GRANT DATE

D. TITLE

Use of reagents for the preparation of a medicine useful for the two stage perioperative therapy of solid tumours"

L. ABSTRACT

The present invention describes the use of an agent endowed with tumour tropism in combination with another agent with anticancer activity and with an affinity for the first agent for the preparation of a medicine useful for the two stage perioperative therapy of solid tumours. The advantages of the present invention consist in the greater, effective localisation of its anticancer activity, in the reduction of the number of administration stages and in the possibility of reducing the anticancer doses, with a resulting decrease in side effects, but without any loss of efficacy.

M. DRAWING

(duty stamp)

Description of the invention entitled:

"Use of reagents for the preparation of a medicine useful for the two stage perioperative therapy of solid tumours"

in the name of: SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A.

nationality: Italian

with registered office in: Viale Shakespeare, 47 - 00144 Roma RM

Inventors: Giovanni PAGANELLI

Paolo CARMINATI

Umberto VERONESI

The present invention relates to the use of reagents for the preparation of a medicine useful for intra and postoperative locoregional and systemic therapy.

Background to the invention

Conservative surgery with axillary dissection and supplementary radiotherapy is the treatment of choice in patients with small sized breast cancers. The results of recent clinical trials, particularly randomised trials (*U. Veronesi, et al., New Engl. J. Med., 305:6-11, 1981; U. Veronesi, et al., Ann. Surg. Vol. 211, 3:250-259, 1990*), have shown that the risk of local recurrence of the tumour correlates with the extent of the operation on the breast, with the patient's age, and with the presence of an extensive intraductal component and peritumoral lymphatic and/or vascular invasion. In addition, a reduced incidence of local recurrence has been demonstrated in subjects undergoing supplementary radiotherapy (5.4% as against 21.6% in the control group) .

The supplementary external radiotherapy currently used after surgical quadrantectomy involves the administration of a total dose of 50-60 Gy in 6 weeks of treatment, with irradiation of the entire residual breast after surgery and possibly an overdose on the operative bed. This kind of treatment regimen has by no means negligible psychological implications; its long duration increases and prolongs the patient's state of

anxiety related to her experience of the disease and leads her to believe that the surgical operation has not been successful in resolving the disease. Moreover, there is also a by no means negligible social impact in terms of costs, related to the patient's absence off work for a period of about 2 months.

As an alternative to traditional radiotherapy treatment Intraoperative Radiotherapy (IORT) has recently been proposed, which is a radiotherapy technique that makes it possible to deliver a single dose of radiation directly to the tumour exposed during surgery, or to the anatomical area that contained the tumour after surgical removal of the cancer. The inventors of the present invention have used IORT with satisfactory results in the context of a randomised study for the treatment of stage T1 cancer of the breast. From the logistic point of view, however, only in a very few centres is it possible to implement this type of therapy; the cost of the equipment alone is more than one million euros, without considering the architectural costs of constructing a shielded operating theatre to guarantee radioprotection for the operators and people in the adjacent rooms and of the specialist staff necessary for implementing the treatment.

A radioimmunotherapy protocol called three step radioimmunotherapy is known, the details of which are described in the *European Journal of Nuclear Medicine Vol. 26, No. 2, February 1999, pp.110-120* e *No. 4, April 1999, pp.348-357* and in European Patent EP 0 496 074. In this method, a reagent kit is used in a form suitable for intravenous administration, consisting of 1) a biotinylated monoclonal antibody specific for an antigen associated with a tumour, 2) a protein of the avidin type, 3) biotin or one of its derivatives conjugated with an efficacious agent for the treatment and/or diagnosis of a tumour. Useful agents for reducing the circulating levels of biotinylated antibody and of proteins of the avidin family (chasing agents) have also been described in the three step radioimmunotherapy method. Such kits are indicated for intracavitary or systemic administration, but no suggestions are provided with regard to sequential administration including both the surgical act and postoperative systemic treatment.

The three-step method is undoubtedly valid in its general description, but it can be optimised and further exploited if large amounts of avidin are introduced onto the tumour or in areas of the body which could receive or which already harbour residual tumour cells after an apparently radical operation. The two main limitations of the classic three-step method consist in the fact that only modest amounts of antibodies and proteins of the avidin family, most frequently streptavidin (steps 1 and 2) reach the target after intravenous inoculation. The locoregional inoculation is applicable in natural anatomical cavities such as the peritoneum, pleura, or bladder, or in postoperative virtual cavities as in the case of brain tumours.

Summary of the invention

It has now been found that a perioperative-type approach, including an intraoperative locoregional stage and a second postoperative systemic stage, is particularly advantageous in controlling local recurrences, and, surprisingly, it has been seen that local therapy can be advantageously administered in only two stages, the first of which is performed intraoperatively in a locoregional site and the second postoperatively via a systemic route.

The introduction, during surgery, of an agent endowed with tumour tropism, that is to say, capable of concentrating locally on the tumour cell or in the vicinity of it, immediately prepares, in the residual tissue around the tumour, a sort of receptor of our choosing ready to receive, locally and in an extremely high concentration, the subsequent dose of actual anticancer agent administered intravenously. The anticancer agent must be suitably directed to the site of the tumour, exploiting the affinity of the carrier agent for the receptor artificially created.

Therefore, one first subject of the present invention is the use of a first agent endowed with tumour tropism in combination with a second anticancer agent endowed with affinity for said first agent as active ingredients for the preparation of a medicine useful for two-stage perioperative therapy, the first stage of which consists in an intraoperative locoregional step

and the second in a postoperative systemic step. In one preferred realisation of the invention, the therapy will take the form of radiotherapy.

Another subject of the present invention is a pharmaceutical composition containing said active ingredients in separate containers (kits) suitable for sequential locoregional and systemic administration, said composition constituting a medicine useful for the adjuvant perioperative therapy of operable or not completely removable solid tumours, such as, for instance, cancers of the breast, pancreas, lung, pleura, peritoneum, face and neck, bladder, brain and others.

Advantageously, the present invention solves the problems existing in the present state of the art outlined above. An additional advantage inherent in the increased accumulation of the agent endowed with tumour tropism in the tumour site may consist in the possible reduction of the amount of anticancer agent used.

Detailed description of the invention

In a first preferred realisation of the invention, the therapy is immunotherapy and particularly radioimmunotherapy. Within the context of this first realisation, the agent endowed with tumour tropism is a biotinylated antibody specific for antigens associated with a tumour,.

According to the present invention, in the intraoperative stage, the biotinylated antibody is administered, followed by avidin, thus constructing the “artificial receptor” for the subsequent actual anticancer agent. In this case, the anticancer agent will be carried by biotin, which will be contained in a chemical compound suitable for forming a complex with the anticancer agent and hereinafter referred to as biotin complex, and which will be administered systemically in the postoperative stage.

Biotin, in fact, concentrates locally only where avidin is present and in this case one can be certain that avidin is present in the area one intends to treat, in that it was introduced by the surgeon a few hours earlier (e.g. from 4 to 72 hours) during the operation. This is a further advantage of the present invention as compared to therapy in general, in that it

drastically reduces the time elapsing between removal of the primary tumour and subsequent adjuvant therapy.

The biotinylated antibody is preferably a monoclonal antibody. The antibody may be murine, human or, possibly, chimeric. Specific antibodies against antigens associated with tumours are known and available on the market or can be prepared with methods known to experts in the sector, such as, for example, those described in *Trikha M., et al., Monoclonal antibodies as therapeutics in oncology, Current Opinion Biotechnology 2002; 13:609-614*. Examples of antibodies are provided in the above mentioned European Patent EP 0 696 074. In a first preferred realisation, the antibody is antitenascin monoclonal antibody. Chimeric or recombinant antibodies can also be used (*Trikha M., et al., ibid.*).

With a view to achieving maximum biotinylated antibody accumulation capacity in the target area a mixture of biotinylated monoclonal antibodies can be used, directed against different tumour antigens or against proteins of the extracellular matrix, such as tenascin. These proteins are particularly copious within the tumour and thus constitute an ideal target also after removal of the main tumour mass.

Experts in the sector are familiar with antibody biotinylation.

The avidin compound used may be avidin itself which is a commercially available protein. In addition to naturally occurring avidin, other proteins of the same type can be used, e.g. streptavidin, or polymeric derivatives of avidin, streptavidin, or their derivatives with polyethylene glycol (PEG-ylated avidins; *Chinol M., Br. J. Cancer 1998; 78:189-197*).

The anticancer agent, which in this case will be carried by the biotin compound, may be selected from those available in the sector or may be any other anticancer agent. Examples of anticancer agents are chemotherapeutic agents in general, toxins, cytokines, such as IL-2 interferon, TNF, lymphocyte cells and radionuclides, which constitute a preferred example in the present invention.

The radioactive biotin may be biotin itself labelled with a radioactive isotope by means of a special linker.

The radioisotope will be selected in relation to the specific application. Examples of suitable radioisotopes are Fe-52, Mn-52m, Co-55, Cu-64, Ga-67, Ga-68, Tc-99m, In-111, I-123, I-125, I-131, P-32, Sc-47, Cu-67, Y-90, Pd-109, Ag-111, I-131, Pm-149, Re-186, Re-188, At-211, Pb-212, Bi-212, Lu-177. As will be clear from the following description, beta-emitting radioisotopes such as Yttrium.90 or Luthetium.177 are preferred.

Though the present invention is applicable to the radioimmunotherapy of tumours in general, one preferred application is for breast, lung, pleural and peritoneal tumours.

The reagent doses will be determined by the expert in the sector. They will, however, be calculated so as to deliver a dose which is sure to be tumoricidal against its target.

Indicatively, the containers of the various reagents are generally in a form suitable for injectable administration and contain an adequate quantity of reagent. In a preferred realisation form, the container of the antibody will take the form of a special syringe equipped with one or more needles to facilitate infiltration of the tumour bed and surrounding tissue. Conveniently, the container can also be in a form suitable for administration of the antibody as a spray.

Again by way of an example, the avidin container will be suitable for containing an adequate amount of avidin, indicatively in a ratio of 5:1 to the antibody (e.g. 100 mg vs. 20 mg of antibody), possibly diluted in saline solution. In a particularly preferred form, the container will take the form of a special syringe suitable for successive administrations of precise volumes, e.g. 20 ml in the first phase and one or more further aliquots (10 ml) in a second phase of the surgery, e.g. on the resection margins or residues of diseased tissue which cannot be removed surgically because of infiltration of vital organs. Conveniently, the container may also be in a form suitable for the administration of avidin as a spray..

Preferably, the various containers, already containing the doses of the individual active ingredients, will be contained in a single pack (kit) bearing the instructions for the modes of administration.

The biotinylated antibody is administered intraoperatively, and after a certain amount of time, e.g. 10 minutes, different doses of avidin are administered, e.g. a first dose in the tumour bed, and a second dose after a possible reconstruction intervention..

Similarly, in a subsequent realisation of the invention, avidinated antibody or avidinated antibody derivatives can be administered directly. There is a method described in the patent application filed by Neorx EP 0 251 494, in which a number of antibody derivatives are used systemically. The present invention differs from that method in that the stage leading to the accumulation of avidin in the tumour site occurs in the operative stage via the locoregional route, whereas only the administration of the biotinylated drug occurs in the postoperative stage. With this procedure a kind of “artificial receptor” is created, capable of taking up radioactive biotin.

From a minimum of 4 hours to 2-3 days postoperatively, the patient will be accompanied to the nuclear medicine department to start the postoperative therapeutic stage with radiolabelled biotin administered systemically. As an alternative to radiolabelled biotin, the biotin can be used as a vehicle for anticancer agents, such as, for example, chemotherapeutic agents or toxins or anticancer cells (e.g. the patient's lymphocytes). (DOTA)-⁹⁰Y/¹⁷⁷Lu biotin will always be administered intravenously. The initial activity will be 50 mCi, for ⁹⁰Y and 80 mCi for ¹⁷⁷Lu. On the basis of previous experience with radioimmunotherapy, these activities are 1/3 less than the maxim activity that can be administered per cycle. The therapeutic window, therefore, may range from 50 to 100 mCi for ⁹⁰Y and from 80 to 150 mCi for ¹⁷⁷Lu. Before administering the radioactive biotin, a “chaser” of biotinylated albumin can be administered, as described in the above mentioned studies by Paganelli *et al.* and in EP 0 496 074, particularly, a fixed dose of 25 mg of biotinylated albumin, 10-15 minutes earlier.

Similarly, in another realisation of the invention, avidin can be directly administered during the intraoperative locoregional phase, since it is endowed with a certain amount of tumour tropism and therefore concentrates in the therapeutic target sites.

Following these simplified procedures, many tumours that do not present specific antigens could still be treated with the reagents avidin and biotin. The sequence of the subsequent events then remains unchanged, through the time interval elapsing between the operation and the systemic therapy, which must be reduced to 424 hours, because the accumulation in the tumour site may require less time. The systemic administration of radiolabelled biotin or carrier agent with anticancer activity will take place as described above.

In another of its realisations, the present invention also provides for the use of the above mentioned active ingredients for the preparation of a diagnostic composition for pretherapeutic biodistribution (dosimetric diagnostic phase), in which the second agent is radiolabelled. In the case of the use of beta and gamma emitters (e.g. Lu 177) such as biotinylated drugs, the dosimetric phase can be carried out at the same time as the therapeutic phase.

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CLAIMS

1. Use of a first agent endowed with tumour tropism in combination with a second anticancer agent endowed with affinity for said first agent as active ingredients for the preparation of a medicine useful for the two stage perioperative therapy of solid tumours.
2. Use according to claim 1, in which said agent endowed with tumour tropism contains one or more antibodies specific for antigens associated with a tumour.
3. Use according to claim 2, in which the antibody or antibodies in said medicine are biotinylated and are in combination with an avidin compound and said second agent is a biotin compound bearing an anticancer agent.
4. Use according to claim 2, in which the antibody in said medicine is avidinated and is in combination with a biotin compound bearing an anticancer agent.
5. Use according to one of claims 2,4, in which said one or more antibodies are monoclonal, and possibly chimeric or recombinant.
6. Use according to one of claims 2,5, in which said antibody is antitenascin.
7. Use according to claim 2, in which said first agent is avidin and said second agent is a biotin compound bearing an anticancer agent.
8. Use according to any of the foregoing claims, in which said anticancer agent is selected from the group consisting of radioisotopes, chemotherapeutic agents, toxins and anticancer cells.
9. Use according to claim 8, in which said radioisotope is selected from the group consisting of Fe-52, Mn-52m, Co-55, Cu-64, Ga-67, Ga-68, Tc-99m, In-111, I-123, I-125, I-131, P-32, Sc-47, Cu-67, Y-90, Pd-109, Ag-111, I-131, Pm-149, Re-186, Re-188, At-211, Pb-212, Bi-212, and Lu-177.
10. Use according to claim 12, in which said radioisotope is Y-90 or Lu-177.
12. Use according to claim 3, in which the biotinylated antibody, the avidin compound and the biotin compound in said medicine are in separate containers.

13. Use according to claim 4. in which the avidinated antibody and the biotin compound in said medicine are in separate containers.
14. Use according to claim 7, in which the avidin and the biotin compound in said medicine are in separate containers.
15. Use according to one of the foregoing claims, in which said tumour is selected from the group consisting of breast, pancreas, lung, pleural, peritoneal, cervicofacial, brain and bladder tumours.
16. Use according to one of claims 3-14, in which said avidin is selected from the group consisting of avidin, streptavidin, their polymeric derivatives and their derivatives with polyethylene glycol.
17. Use according to one of the foregoing claims, in which said medicine is suitable for injectable administration.
18. Use according to claim 17, in which the container of said antibody is in the form of a syringe equipped with one or more needles.
19. Use according to one of claims 12-14, in which the container of said antibody is suitable for administration in the form of a spray.
20. Use according to claim 12, in which said antibody or mixture of antibodies is contained in a first separate container in a single dose.
21. Use according to claim 12, in which said avidin is contained in a second separate container in a single dose.
22. Use according to claim 3, in which the amount of avidin in said medicine is in a ratio 5-10 times higher than the amount of antibody or mixture of antibodies.
23. Use according to claim 12, in which the container of said avidin is in the form of a syringe suitable for successive administrations of precise volumes.
24. Use according to claim 7, in which said avidin is contained in a separate container in a single dose.

25. Use according to claim 7, in which the container of said avidin is suitable for administration in the form of a spray.
26. Kit for two-stage adjuvant intra- and peri-operative locoregional and/or systemic therapy, containing a set of separate containers, in which the first container contains a biotinylated antibody specific for antigens associated with a tumour or a mixture of antibodies, the second container contains an avidin compound, the third container contains a biotin compound bearing an anticancer agent, and there may possibly be a fourth container containing biotinylated albumin.
27. Kit for two-stage adjuvant intra- and peri-operative locoregional and/or systemic therapy, containing a set of separate containers, in which the first container contains an avidinated antibody specific for antigens associated with a tumour or a mixture of avidinated antibodies, and the second container contains a biotin compound bearing an anticancer agent.
28. Kit for two-stage adjuvant intra- and peri-operative locoregional and/or systemic therapy, containing a set of separate containers, in which the first container contains an avidin compound, and the second container contains a biotin compound bearing an anticancer agent.
29. Use of a first agent endowed with tumour tropism in combination with a second radiolabelled agent endowed with affinity for said first agent for the preparation of a diagnostic composition for the pretherapeutic biodistribution of the medicine according to claim 1.

on behalf of SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A.

Dott. Marco Spadaro

(signature)

Seal